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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

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— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
28 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTION DERIVATIVES OF N⁶-BENZYLADENOSINE, METHODS OF THEIR PREPARATION, THEIR USE FOR PREPARATION OF DRUGS, COSMETIC PREPARATIONS AND GROWTH REGULATORS, PHARMACEUTICAL PREPARATIONS, COSMETIC PREPARATIONS AND GROWTH REGULATORS CONTAINING THESE COMPOUNDS

(57) Abstract: The invention concerns novel substitution derivatives of N⁶-benzyladenosine having anticancer, mitotic, immuno-suppressive and antisenescent properties for plant, animal and human cells. This invention also relates to the methods of preparation of these N⁶-benzyladenosine derivatives and their use as drugs, cosmetic preparations and growth regulators comprising these derivatives as active compound and use of these derivatives for preparation of pharmaceutical compositions, in biotechnological processes, in cosmetics and in agriculture.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/CZ 03/00078	29/12/2003	30/12/2002
Applicant		
USTAV EXPERIMENTALNI BOTANIKY AKADEMIE ...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CZ 03/00078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14 (in part)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where R1 is hydrogen, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto.

2. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is hydroxyl, alkoxy, acyloxy or carbalkoxy, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto.

3. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is halogen, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

4. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is amino, hydrazo, nitro, amido, acylamino, alkylamino or dialkylamino, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

5. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is mercapto, methylmercapto or alkylmercapto, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

6. claims: 1-14 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is carboxyl, cyano or carbamoyl alkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

7. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is sulpho or sulphamido, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

8. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is cycloalkyl, substituted cycloalkyl or cycloalkylalkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

9. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is substituted alkyl or arylalkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

10. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is heteroalkyl, heteroarylalkyl or cycloheteroalkyl alkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

11. claims: 1-14 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is R1'-X with R1' and X as defined in claim 1, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto insofar as this subject does not fall within one of the earlier subjects.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CZ 03/00078

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/16 A61Q19/08 A61K8/49 A61K31/7076 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61Q A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 781 273 A (FAULAND E ET AL) 25 December 1973 (1973-12-25) N6-benzyladenosine the whole document -----	1-4,7,9, 14
A	DUTTA S P ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITES OF SOME N-(NITRO-AMINOBENZYL) ADENOSINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 18, no. 8, 1 August 1975 (1975-08-01), pages 780-783, XP000653225 ISSN: 0022-2623 compounds 2-4,6-9,11 the whole document ----- -/-	1-5,7,9, 12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

^o Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

12 May 2004

26.08.2004

Name and mailing address of the ISA

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de Nooy, A

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRESSI J C ET AL: "ADENOSINE ANALOGUES AS INHIBITORS OF TRYPANOSOMA BRUCEI PHOSPHOGLYCERATE KINASE: ELUCIDATION OF A NOVEL BINDING MODE FOR A 2-AMINO-N6-SUBSTITUTED ADENOSINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 22, 2000, pages 4135-4150, XP000999137 ISSN: 0022-2623 compounds 27a,b the whole document -----	1-4,7,9, 14
X	M.H. FLEYSHER ET AL.: "Synthesis and biological activity of some new N6-substituted purine nucleosides" J. MED. CHEM., vol. 12, 1969, pages 1056-1061, XP002280031 N6-benzyladenosine the whole document -----	1-5,7,9, 12
X	US 3 551 409 A (DIETMANN KARL ET AL) 29 December 1970 (1970-12-29) examples 6 and 55 the whole document -----	1-4,7,9, 14
X	EP 0 540 854 A (SANSHO SEIYAKU KK) 12 May 1993 (1993-05-12) page 10, N6-benzyladenosine the whole document -----	1-3,6
X	WANNER M J ET AL: "2-Nitro analogues of adenosine and 1-deazaadenosine: synthesis and binding studies at the adenosine A ₁ , A _{2A} and A ₃ receptor subtypes" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 18, September 2000 (2000-09), pages 2141-2144, XP004208330 ISSN: 0960-894X compound 9d the whole document -----	1-4,7,9, 14
X	TRIVEDI B K ET AL: "C ₂ N ₆ -DISUBSTITUTED ADENOSINES: SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 32, 1989, pages 1667-1673, XP002053657 ISSN: 0022-2623 compounds 52 and 53 the whole document -----	1-4,7,9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CZ 03/00078

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MAGYAR-TABORI ET AL.: "High in vitro shoot proliferation in the apple cultivar jonagold induced by benzyladenine analogues" ACTA AGRONOMICA HUNGARICA, vol. 50, 2002, pages 191-195, XP008030626 N6-benzyladenosine the whole document -----	1-5,7, 10,12,13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CZ 03/00078

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